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Logical formulation development for Furosemide dissolution enhancement by preparing solid dispersion containing adsorbent

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Abstract

Furosemide, a weekly acidic, loop diuretic drug indicated for treatment of edema and hypertension having high permeability through stomach because it remain 99.8 % unionize in stomach (pKa of Furosemide 3.9, pH of gastric fluid-1.2). Furosemide is practically insoluble in stomach medium (0.006 mg/mL) and having highly permeability through stomach but due to its solubility limitation it can't enter in to systemic circulation. Gastric empting time is ranging from 30 min to 2 hrs after this time it goes in to small intestine where it is soluble but can't permeate through its membrane due to its permeation limitation (furosemide having pH depended solubility and permeability). Furosemide available in dose of 20 mg, 40 mg and 80 mg tablets. In present work, 40 mg furosemide was taken. Solubility depends on amount of solute, amount of solvent, temperature, stirring speed, time and other factors. Due to low dose of drug it can be dissolves within gastric empting time if solubility enhancing excipients added. It was logically decided to design experiments, so as to achieve the set objectives. Thus, an attempt was made to prepare solid dispersion of furosemide with Poly ethylene glycol (PEG) 6000 containing microcrystalline cellulose (MCC) as adsorbent which would dissolve completely in less than 30 minutes (target selected by considering minimum gastric empting time). These attempts improve bioavailability and consequently dose reduction would possible.

Keywords: Furosemide, PEG 6000, solid dispersion, Micro crystalline cellulose, dissolution.

INTRODUCTION

Recently more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water. Formulation of poorly soluble compounds for oral delivery now presents one of the interesting challenges to formulation scientists in the pharmaceutical industry. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°C, due to erratic or incomplete absorption from GIT [1].

In the Present Investigation, drug which is practically insoluble in gastric fluid and having high permeability through stomach was selected. The rational for selecting such type is "Drug which having highly permeability through stomach but due to its solubility limitation in gastric fluid it can't enter in to systemic circulation. Gastric empting time is ranging form 30 min to 2 hrs after this time drugs go in to small intestine where it is soluble but can't permeate through its membrane due to its permeation limitation." To improve dissolution of such drug is challenging and rational. furosemide is one of them. furosemide is a weekly acidic, non-steroidal anti inflammatory drug having high permeability through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric empting time is ranging from 30 min to 2 hr , after this time furosemide goes in to small intestine where it is solubilise but can't permeate through its membrane. To improve dissolution of such drug is challenging and rational. In present investigation, dissolution of furosemide improves by preparing floating granules.

Furosemide, a weekly acidic, loop diuretic drug indicated for treatment of edema and hypertension having high permeability through stomach because it remain 99.8 % unionize in stomach [2] (pKa of Furosemide 3.9, pH of gastric fluid - 1.2). Furosemide is practically insoluble in stomach medium (0.006 mg/mL) and having highly permeability through stomach but due to its solubility limitation it can't enter in to systemic circulation. Gastric empting time is ranging from 30 min – 2 hrs [3] after this time it goes in to small intestine where it is soluble but can't permeate through its membrane due to its permeation limitation (furosemide having pH depended solubility and permeability).

MATERIALS AND METHODS

Materials

Furosemide Gifted by Torrent Research centre, Ahmedabad and Poly ethylene glycol (PEG) 6000, Micro crystalline cellulose purchased from S. D. fine chemicals, Mumbai. Empty Hard gelatine capsules gifted from Astron Research Ltd., Ahmedabad. All other chemicals and reagents used are of analytical grade.

Method

Solid dispersion prepare by fusion method. PEG 6000 melted in porcelain dish. Drug was dispersed in molted PEG 6000 then immediately Micro Crystalline Cellulose as adsorbent was added in porcelain dish (Microcrystalline cellulose having an excellent adsorbent property which converted sticky dispersions in to free flow powder with improved surface area which assisted in dissolution enhancement). Amount of PEG 6000 and adsorbent added as shown in following Table 1. 2-factor, 3-level central composite design and optimization process for floating granules of furosemide was employed. Amount of PEG 6000 (A) and amount of adsorbent (B) were selected as the independent variables whereas angle of repose and T100% (time require to dissolve 100% drug) were selected as dependent variables (Response).

In Vitro Dissolution

Dissolution of prepared formulations (equivalent to 40 mg of furosemide) was performed in 900 ml 0.1 N HCl (pH 1.2) in USP type-II Dissolution apparatus at 50 RPM., Dissolution medium was kept at 37 + 0.5 ^{0}C. 5 ml sample were collected at different time interval and filtered through a whatman filter paper (0.45 µm). The same amount of fresh dissolution medium was added to maintain sink condition. The absorbance was measured at 220.5 nm

using UV-visible spectrophotometer. The concentration of furosemide was calculated by using standard curve equation.

Table 1. Design Data for 3^2 factorial designs

Formulation code	Amount of PEG 6000 in mg (A)	Amount of Adsorbent in mg (B)
F1	80	150
F2	80	200
F3	80	250
F4	120	150
F5	120	200
F6	120	250
F7	160	150
F8	160	200
F9	160	250

Data Analysis

The response surface methodology is a collection of mathematical and statistical techniques used for modelling and analysis of problems in which a response of interest is influenced by several variable and the objectives is to optimize this response. The run or formulation, which are designed based on factorial design were evaluated for the response. The response values are subjected to multiple regression. Analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis were Angle of repose and T100%. The multiple regression analysis was done using DESIGN EXPERT 7.1.6 (STAT-EASE) demo version software, which specially meant for this optimization process. Analysis of data was carried out using ANOVA and the individual parameter was evaluated with F-test. Using the regression coefficient of factor, the polynomial equation for the each response was generated [4].

Formulations Optimization by Factorial Design

The computation for optimized formulation was carried using software, DESIGN EXPERT 7.1.6 (STAT-EASE). The response variable considered for optimization were Angle of repose and T1000%. The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). Constraints for responses and factors are shown in Table 2.

Table 2. Constraints for optimization

Name	Goal	Lower Limit	Upper Limit
Amount of PEG 6000	In range	80 mg	160 mg
Amount of Adsorbent	In range	150 mg	250 mg
Angle of repose	Target < 30.	23	45
T100%	Target = 30 minute	30	165

By utilizing DESIGN EXPERT 7.1.6 (STAT-EASE) demo version software, one solution for optimized formulation. The optimized formulation is prepared and evaluated for angle of repose and T100%. Observe response value of the optimized formulation was compared with predicted value.

RESULTS AND DISCUSSION

In Vitro Dissolution

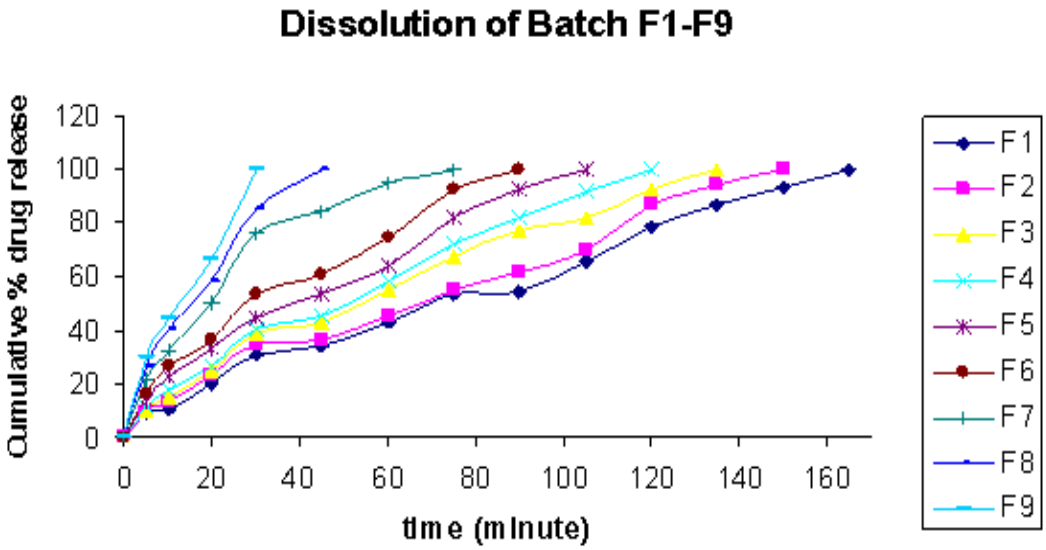

Figure 1. Dissolution comparison of Batch F1-F9

Dissolution comparison of Batch F1-F9 shown in Fig. 1. In batch F1, F2 and F3 same amount of PEG 6000 (80 mg) present with differ amount of Adsorbent (150 mg, 200 mg and 250 mg present in F1, F2 and F3 respectively). 165 minutes, 150 minutes and 135 minutes required to dissolve 100% drug in batch F1, F2 and F3 respectively. It was indicated as the amount of adsorbent increase, T100% decrease proportionally that was due to MCC is adsorbent that convert sticky furosemide-PEG 6000 solid dispersion in to free flow powder hence surface area was increase which improve dissolution.

Similar to F1, F2 and F3, amount of adsorbent was in increasing order in F4, F5, F6 and F7, F8, F9.

In the comparison of Batch F3, F6 and F9 (same amount of adsorbent with differ amount of PEG 6000. 80 mg, 120 mg and 160 mg PEG 6000 present in Batch F3, F6 and F9 respectively), order of T100% was F3<F6<F9. It indicated as the amount of PEG 6000 increase T 100% decrease that was due to PEG 6000 is high molecular weight, hydrophilic polymer which disperse drug at molecular level and convert crystalline furosemide into amorphous form.

Data Analysis

A 3^2 Factorial design was adopted, using the amount of PEG 6000 (A) and amount of microcrystalline cellulose (B) as independent variables. The response (Y) values subjected for this analysis are angle of repose and T100%.

The responses (**Angle of repose and T $_{100\%}$**) were recorded and analysis of data was carried out using ANOVA in (STAT-EASE). The individual parameter was evaluated using F-test and a polynomial equation for each response was generated using MLRA. The design and response summary data are represented in Table 3.

Table 3. The design and response summary data

Formulation code	Factor		Response	
	Amount of PEG 6000 in mg	Amount of Adsorbent in mg	Angle of repose	T100%
F1	80	150	37	165
F2	80	200	29	150
F3	80	250	23	135
F4	120	150	42	120
F5	120	200	33	105
F6	120	250	26	90
F7	160	150	45	75
F8	160	200	38	45
F9	160	250	29	30

Response 1: Angle of repose

$$Y = b_0 + b_1A + b_2B + b_{11}A^2 + b_{22}B^2 + b_{12}AB$$

where Y is the response, b_0 is the intercept, A and B are the independent factors, b_1 and b_2 are coefficients of independent factors. The coefficients with second order terms (b_{11} and b_{22}) indicate the quadratic nature and b_{12} is the interaction term (combining effect of independent factors).

Polynomial Equation in Terms of Coded Factors

Angle of repose = +33.44 +3.83A - 7.67B -0.50AB-0.17A^2 +0.33B^2 ____ Equation (1)

It was arbitrarily decided to obtain the values of the angle of repose less than 30 minutes from the formulated products. The results for dependent variable (angle of repose) of the batches are shown in Table 3. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A and B having significant effect on angle of repose.

A coefficient with a positive sign shows a synergistic effect whereas a coefficient with a negative sign shows an antagonistic effect. In Equation (1), A Coefficient of Independent factor A with a positive sign (+3.83 A) indicates as the amount of PEG 6000 increase, angle of repose increase (In Table 3, Formulation F2, F5 and F8) whereas a coefficient of Independent factor B with a negative sign (-7.67 B) indicate as the amount of adsorbent increase, angle of repose decrease (In Table 3, Formulation F4, F5 and F6). The coefficients with second order terms (b11 and b22) indicate the quadratic nature in which a negative sign indicate (-0.17 A^2) as the amount of PEG 6000 added in more amount, angle of repose had to be decrease but here it was increase that may be due to higher amount of PEG 6000 retard powder flow. (In Table 3, compare formulation F3, F6 and F9) whereas a coefficient with a positive sign (+0.33 B^2) indicate as higher amount of adsorbent added, angle of repose had to be increase but here it was decrease that may be due to higher amount of adsorbent make free flow powder (In Table 3 compare formulation F7, F8 and F9).

Above results were never possible in presence of individual Independent factors hence, one cannot draw conclusions by considering the mathematical signs (positive or negative) of the coefficient of Independent factors (b_1 and b_2) and coefficient of the quadratic term (b_{11} and

b_{22}) on the value of angle of repose so combining effect of both of Independent factors was require to predict and achieving targeted value of angle of repose. Negative sign of the interaction term (- 0.50) indicated as the both PEG 6000 and adsorbent increase, angle of repose decrease (In Table 3, compare formulation F1, F5 and F9). The magnitude of b2 (7.67) is greater than b1 (3.83) which indicated the greater influence of Adsorbent comparatively PEG 6000 on angle of repose.

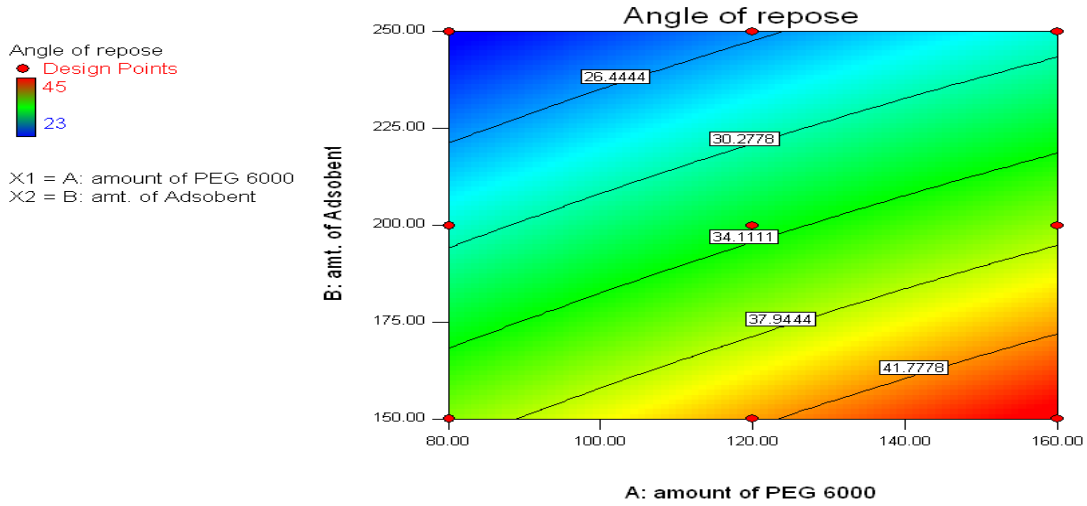

Figure 2. Contour plot showing the effect of amount of PEG 6000 and amount of adsorbent on angle of repose

The relationship between the dependent and independent variables was further elucidated using contour plots. Here, arbitrarily predecided to obtain the values of the angle of repose less than 30 minutes from the formulated products. In contour plot only formulation F9 showed angle of repose near to desired angle of repose (Fig 2, Indicated by light blue colour). The final selection of the optimized batch would be done after considering the other requirements of the dosage form, i.e., T100%.

Response 2: T $_{100\%}$
Polynomial Equation in Terms of Coded Factors:

$T100\% = +103.33 -50.00\ A -17.50B -3.75\ AB -5.00A^2 +2.50B^2$_____ Equation (2)

It was logically decided to obtain the values of the T100% was 30 minutes from the formulated products. The results for dependent variables floating time of the batches are shown in Table 3. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms.

In Equation (2), A Coefficient of Independent factor A with a negative sign (-50 A) indicates as the amount of PEG 6000 increase, T100% decrease (In Table 3, Formulation F2, F5 and F8) similarly a coefficient of Independent factor B with a negative sign (-17.5 B) indicate as the amount of adsorbent increase, angle of repose decrease (In Table 3, formulation F1, F2, F3, formulation F4, F5, F6 and formulation F7, F8, F9). The coefficients with second order terms (b11 and b22) indicate the quadratic nature in which a negative sign indicate (-5.00 A2) as the amount of PEG 6000 added in more amount, T100% decrease (In Table 3, compare formulation F3, F6 and F9) whereas a coefficient with a positive sign (+2.50 B2) indicate as

higher amount of adsorbent added, T100% had to be increase but here it was decrease that may be due to higher amount of adsorbent increase surface area that assist in dissolution (In Table 3 compare formulation F7, F8 and F9).

Above results were never possible in presence of individual Independent factors hence, one cannot draw conclusions by considering the mathematical signs (positive or negative) of the coefficient of Independent factors (b1 and b2) and coefficient of the quadratic term (b11 and b22) on the value of angle of repose so combining effect of both of Independent factors was require to predict and achieving targeted value of angle of repose. Negative sign of the interaction term (- 3.75) indicated as the both PEG 6000 and adsorbent increase, T100% decrease (In Table 3, compare formulation F1, F5 and F9). The magnitude of b1 (50) is greater than b2 (17.5) which indicated the greater influence of PEG 6000 comparatively Adsorbent on T100%.

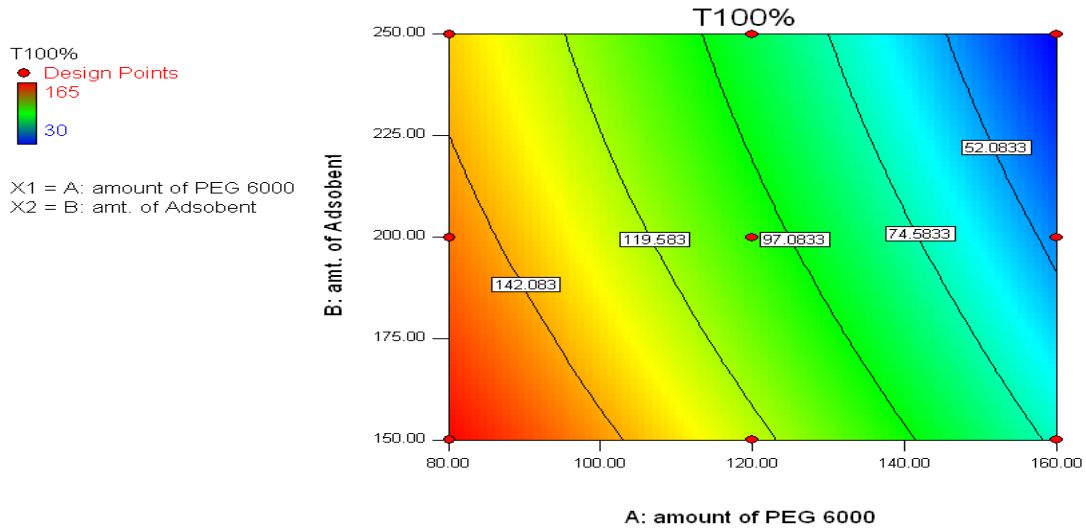

Figure 3. Contour plot showing the effect of amount of PEG 6000 and amount of Adsorbent on T100%

The relationship between the dependent and independent variables was further elucidated using contour plots. Here, logically predecided to obtain the values of the T100% was 30 minutes from the formulated products. In contour plot only formulation F9 showed T100% near to desired T100% (Fig. 3, Indicated by Blue color). Exact amount of PEG 6000 and MCC for achieving desired response was found out from optimization.

Formulations Optimization

For the optimization of solid dispersion of furosemide constraints was fixed for all factors and response (Table 4). Constraints were set according to formulation of solid dispersion using minimum amt of excipients, which would give desired response values. In the present study our aim was T100% achieved in 30 minutes. In optimization (Fig. 4) desirability 1.0 indicated optimum formulation was achieved at 249.56 mg of PEG 6000 and 159.83 mg of MCC. Validation of optimization technique done by preparing checkpoint batch and response were evaluated. The responses value observed in checkpoint batch was very near to optimized batch.

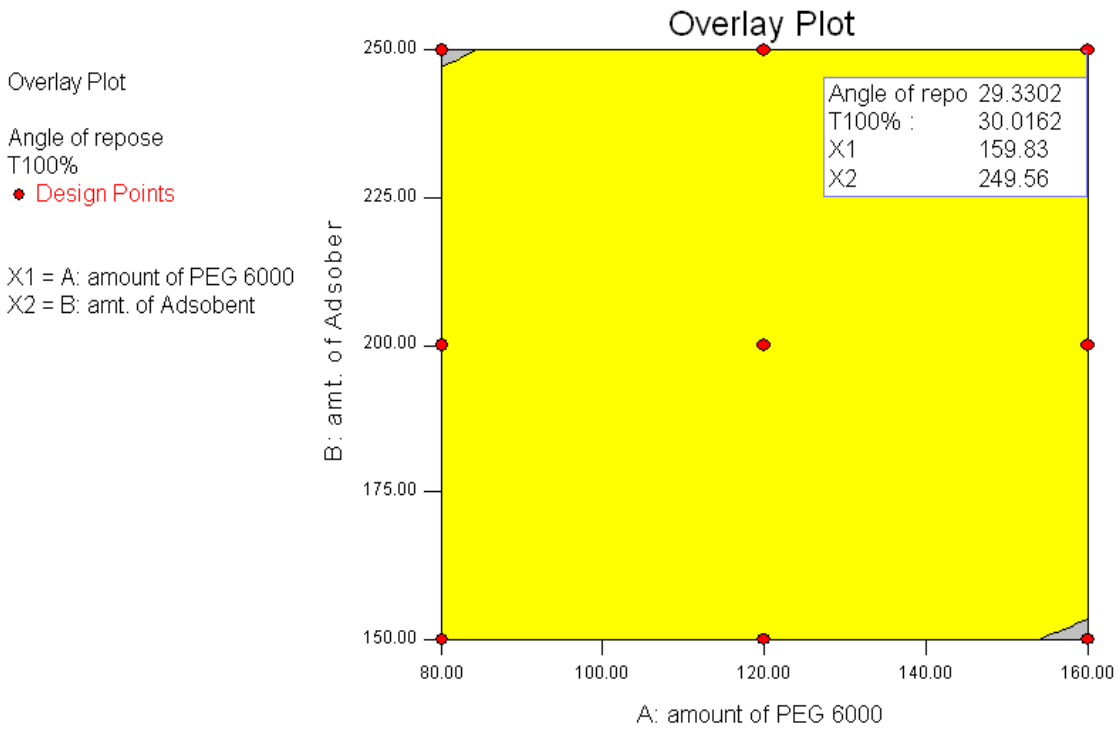

Figure 4. Overlay plot for optimization

CONCLUSION

From above research work it was concluded that for improving dissolution of weakly acidic and those drugs which are mostly absorb through stomach, solid dispersion approach is gold standard but if problem observed in preparing dispersion, addition of adsorbent convert sticky dispersion in to free flow powder hence it is easy to formulate tablets or capsules.

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